Conoscere e Curare il Cuore 2019

GIOVEDI' 28 FEBBRAIO

ATEROSCLEROSI SUBCLINICA: COME E QUANDO TRATTARLA

Laura Gatto

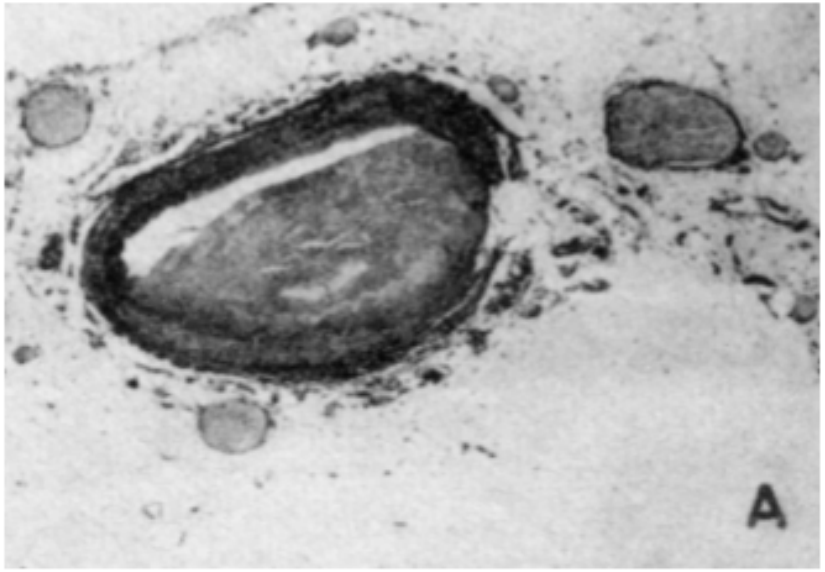
Cardiologia d'Urgenza
A.O. San Giovanni-Addolorata, Roma
Centro per la Lotta contro l'Infarto - Fondazione Onlus, Roma

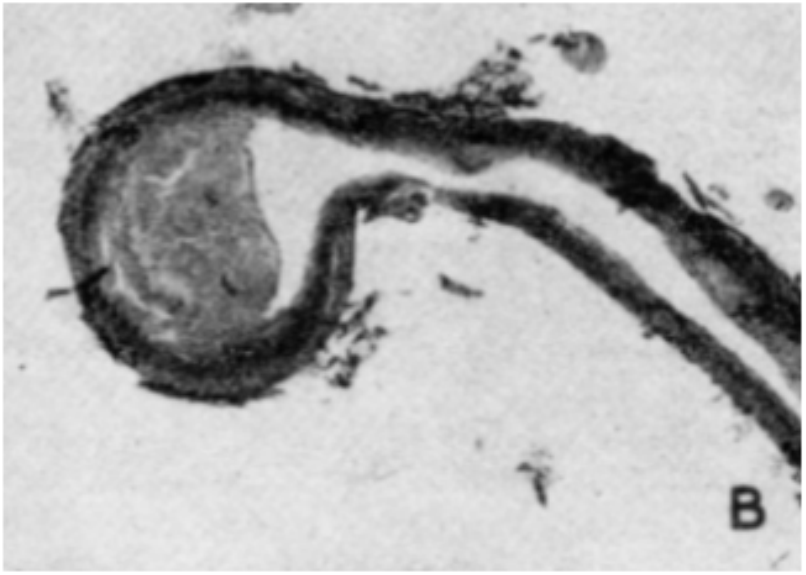
Coronary Disease Among United States Soldiers Killed in Action in Korea

Preliminary Report

Major William F. Enos, Lieut. Col. Robert H. Holmes (MC), U.S. Army and Capt. James Beyer (MC), Army of the U.S.

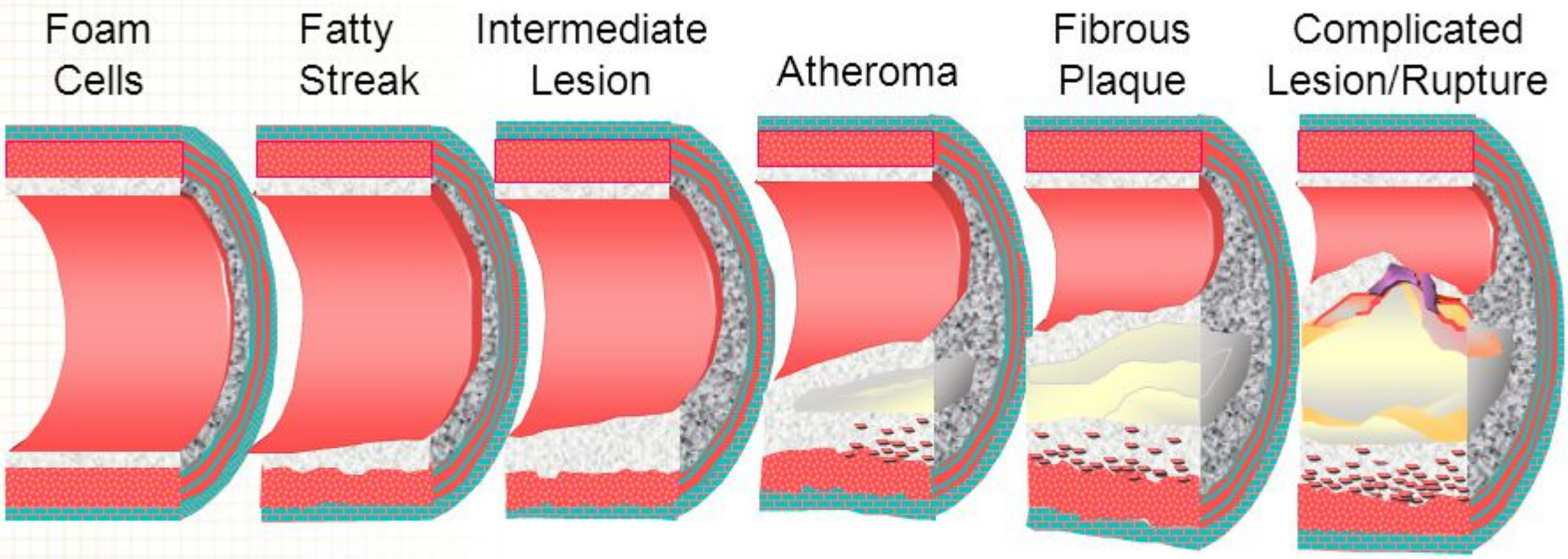
Landmark Article
July 18, 1953
(JAMA 1953;152:1090-1093)





Cross-section of 22 years old soldier's coronary arteries exhibiting significant narrowing from atherosclerotic plaques

Atherosclerosis timeline



Adpated from Stary HC et al, Circulation 1995;92:1355-1374

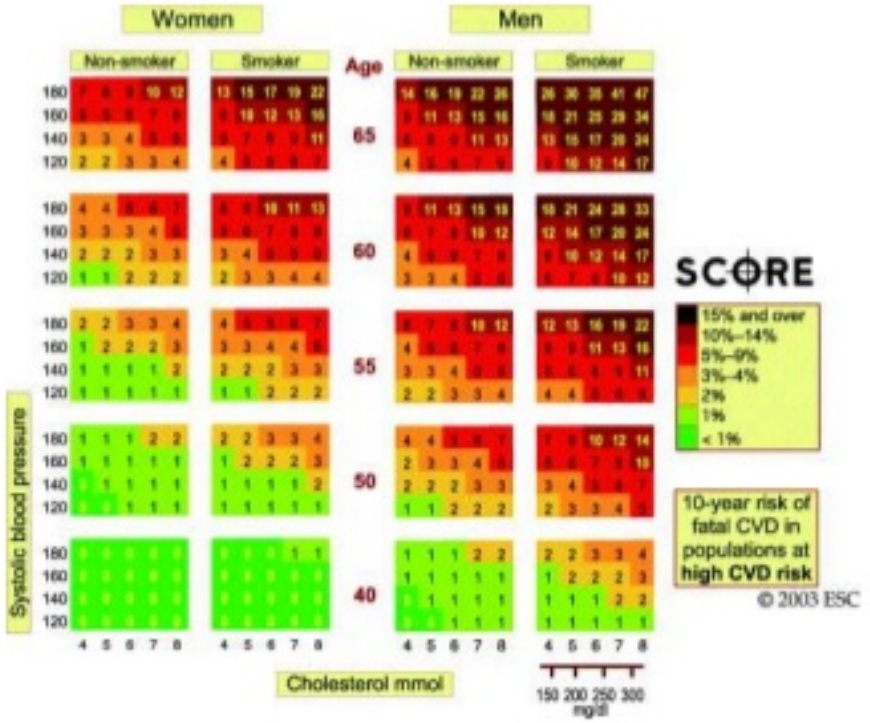
Traditional Cardiovascular Risk Score

FRAMINGHAM

- Age
- Gender
- Smoker
- Total cholesterol
- HDL-C
- Systolic BP
- HTN Rx

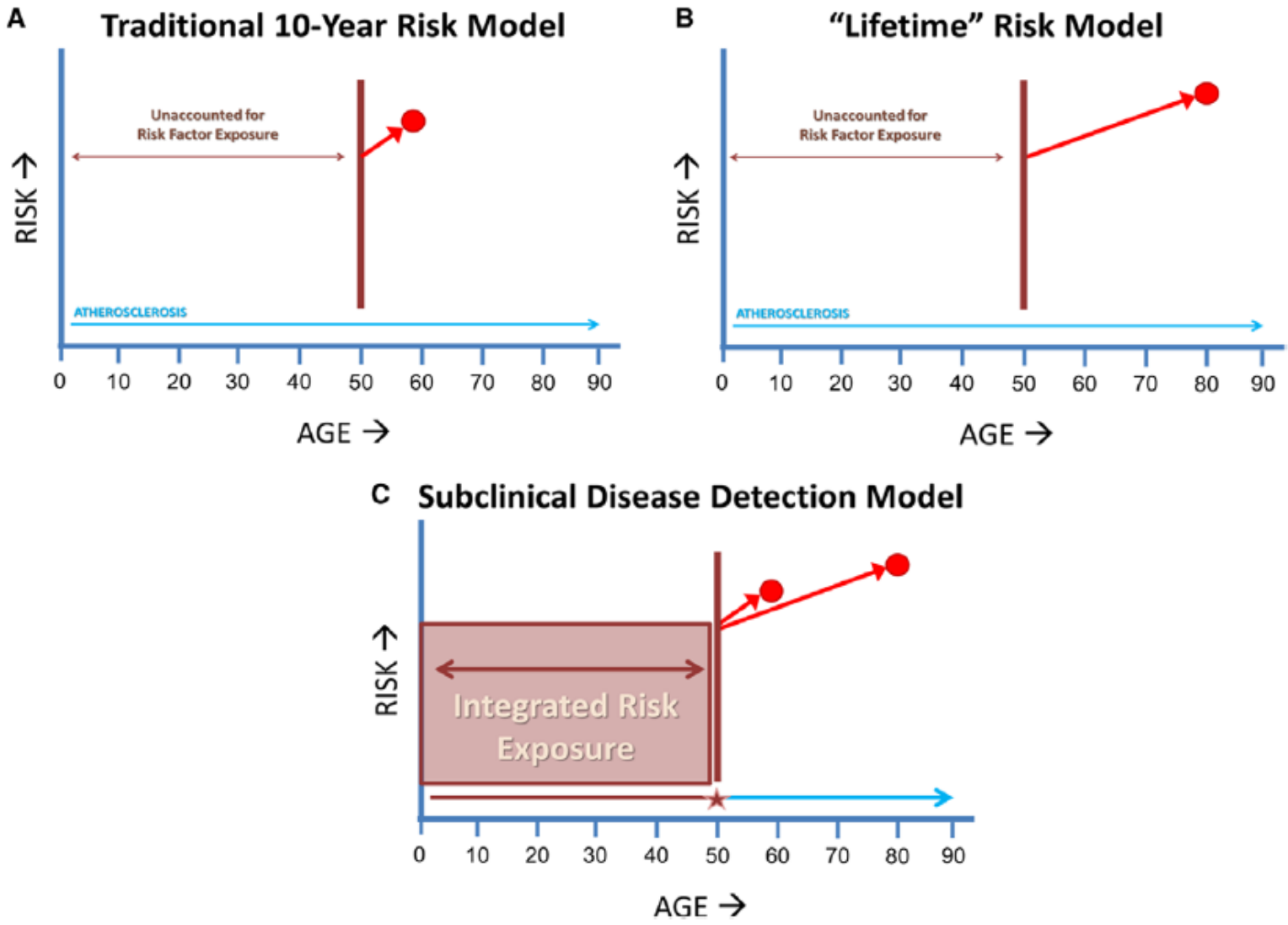
Calculates 10-year risk for CHD death or nonfatal MI

SCORE



High risk: > 20%
Intermediate risk: 10-20%
Low risk: < 10%

But…Clinical Risk Score are not sufficient…



Blaha MJ et al, Circ Cardiov Imaging 2014;7:398-408

Screening for Atherosclerosis

Risk Factors vs Disease

Numerous Risk Factors

- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- ?

Over 200 risk factors have been reported.

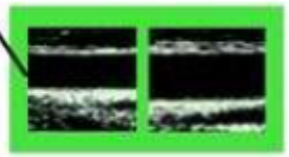
Examples of Arterial Structure Tests

Carotid IMT and Plaque Measured by Ultrasound

Aortic and Carotid Plaque Detected by MRI

Coronary Calcium Score Measured by CT

Ankle Brachial Index



Brachial Vasoreactivity Measured by Ultrasound

Vascular Compliance Measured by Radial Tonometry

Examples of Arterial Function Tests

Microvascular Reactivity Measured by Fingertip Tonometry

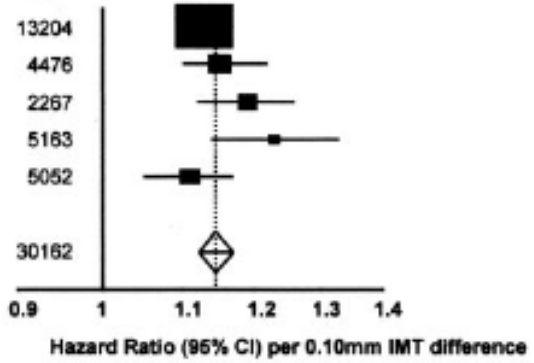
Prediction of Clinical Cardiovascular Events With Carotid Intima-Media Thickness

A Systematic Review and Meta-Analysis

For an absolute carotid IMT difference of 0.1 mm, the future risk of MI increases by 10 to 15% and the stroke risk increases by 13 to 18%

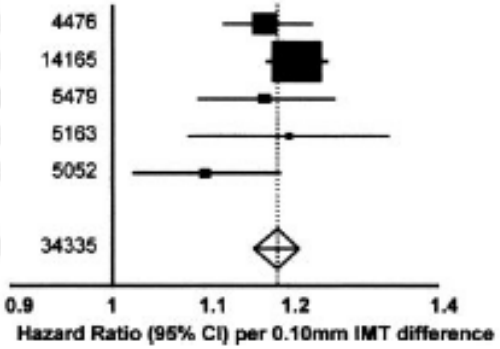
A **Hazard ratio (HR) for MI per 0.1mm difference in CCA-IMT, adjusted for age and sex**

Study	HR	[95% CI]	n	Data source
Atherosclerosis Risk in Communities Study (ARIC)	1.13	[1.10-1.17]	13204	unpublished data
Cardiovascular Health Study (CHS)	1.15	[1.10-1.22]	4476	O'Leary 1999 (5)
Rotterdam Study	1.19	[1.12-1.26]	2267	Del Sol 2002 (7)
Malmö Diet and Cancer Study subcohort (MDCS)	1.23	[1.14-1.33]	5163	Rosvall 2005 (10)
Carotid Atherosclerosis Progression Study (CAPS)	1.11	[1.05-1.17]	5052	Lorenz 2006 (12)
TOTAL	1.15	[1.12-1.17]	30162	
I^2 for heterogeneity	42.5%			



B **Hazard ratio (HR) for stroke per 0.1mm difference in CCA-IMT, adjusted for age and sex**

Study	HR	[95% CI]	n	Data source
Cardiovascular Health Study (CHS)	1.17	[1.12-1.23]	4476	O'Leary 1998 (5)
Atherosclerosis Risk in Communities Study (ARIC)	1.21	[1.17-1.25]	14165	unpublished data
Rotterdam Study	1.17	[1.09-1-26]	5479	Hollander 2003 (8)
Malmö Diet and Cancer Study subcohort (MDCS)	1.20	[1.08-1.33]	5163	Rosvall 2005 (11)
Carotid Atherosclerosis Progression Study (CAPS)	1.10	[1.02-1.19]	5052	Lorenz 2006 (12)
TOTAL	1.18	[1.16-1.21]	34335	
I^2 for heterogeneity	28.2%			

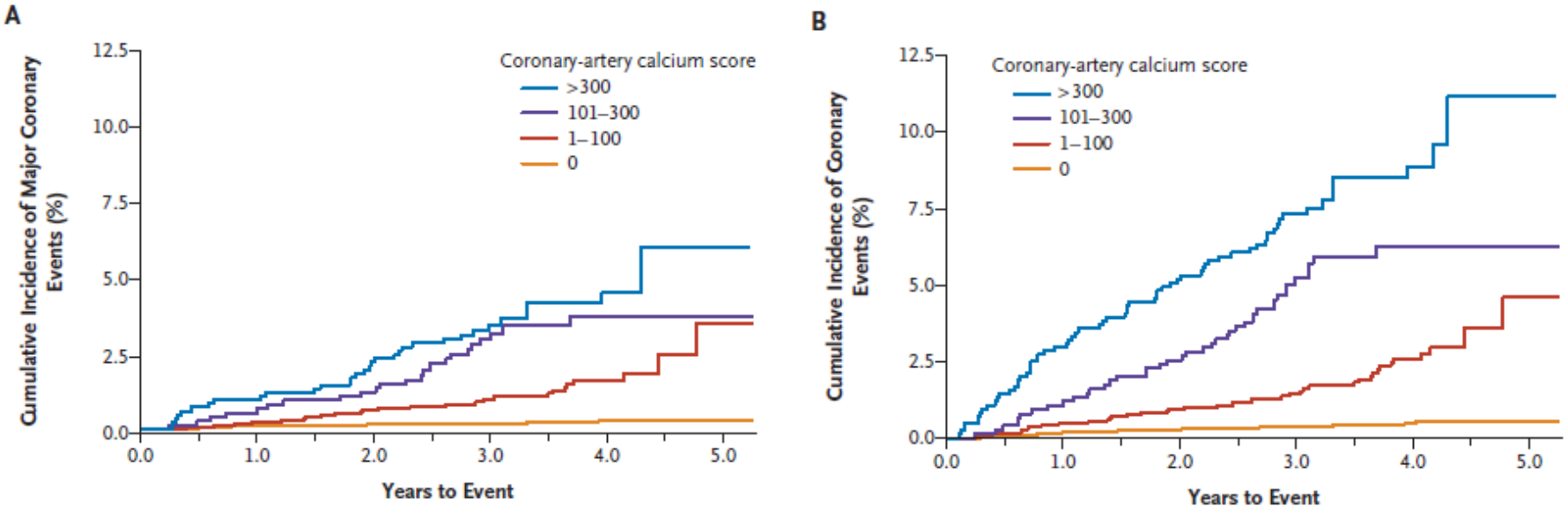


Lorenz MW et al, Circulation 2007;115:459-467

Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Robert Detrano, M.D., Ph.D., Alan D. Guerci, M.D., J. Jeffrey Carr, M.D., M.S.C.E., Diane E. Bild, M.D., M.P.H., Gregory Burke, M.D., Ph.D., Aaron R. Folsom, M.D., Kiang Liu, Ph.D., Steven Shea, M.D., Moyses Szklo, M.D., Dr.P.H., David A. Bluemke, M.D., Ph.D., Daniel H. O'Leary, M.D., Russell Tracy, Ph.D., Karol Watson, M.D., Ph.D., Nathan D. Wong, Ph.D., and Richard A. Kronmal, Ph.D.

6722 participants, with no clinical CVD at baseline and followed for a median of 3.8 years
38.6% white, 27.6% black, 21.9% Hispanic, and 11.9% Chinese

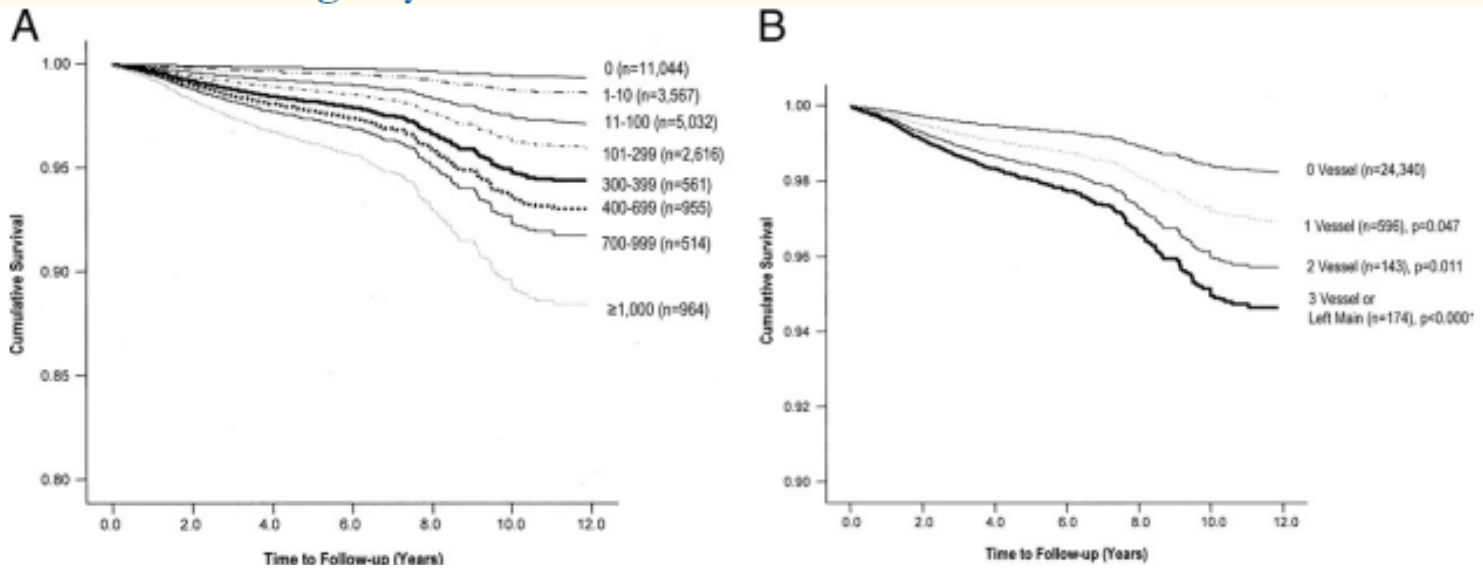


A doubling of the CAC increased the risk of a major coronary event by 15 to 35% and the risk of any coronary event by 18 to 39%

NEJM 2008;358: 1336-45

Long-Term Prognosis Associated With Coronary Calcification

Observations From a Registry of 25,253 Patients



	Relative Risk	95% CI	% of Chi-Square	p Value	C-Index*
Model† 1: CAC score					
Overall	1.31	1.23–1.39	14% (274/2,017)	<0.0001	0.757 (0.728–0.787)
1–10	1.48	0.71–3.07		0.29	
11–100	3.61	2.11–6.18		<0.0001	
101–399*	3.84	2.20–6.68		<0.0001	
400–699	5.78	3.00–11.16		<0.0001	
700–999	6.47	3.37–12.43		<0.0001	
≥1,000	9.36	5.36–16.33		<0.0001	
Model† 2: CAD extent (/vessel)					
Overall	1.58	1.28–1.96	4% (25/677)	<0.0001	0.552 (0.511–0.592)
1-vessel	1.39	0.95–2.03		0.086	
2-vessel	1.85	1.03–3.30		0.038	
3-vessel or left main	2.44	1.58–3.78		<0.0001	

Budoff JM et al., JACC 2007;49: 1860-7

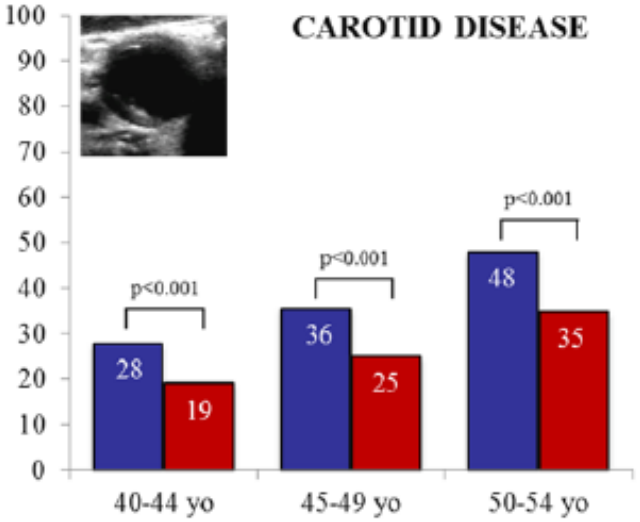
Prevalence, Vascular Distribution, and Multiterritorial Extent of Subclinical Atherosclerosis in a Middle-Aged Cohort

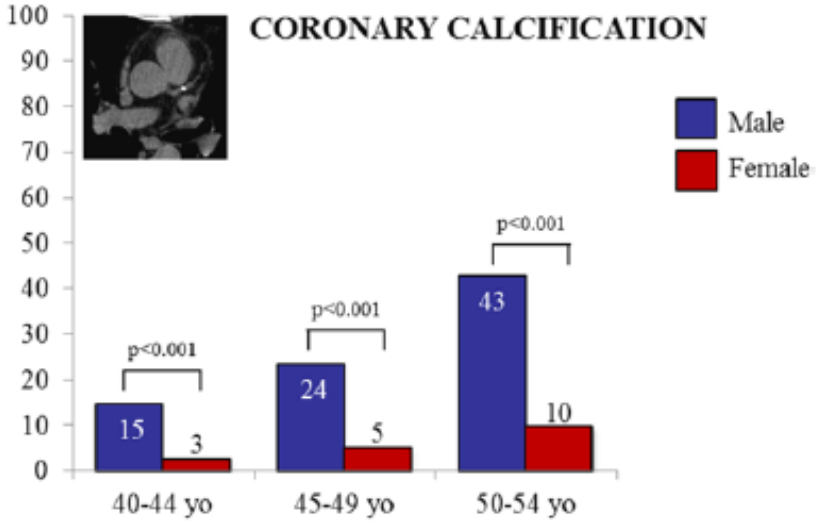
The PESA (Progression of Early Subclinical Atherosclerosis) Study

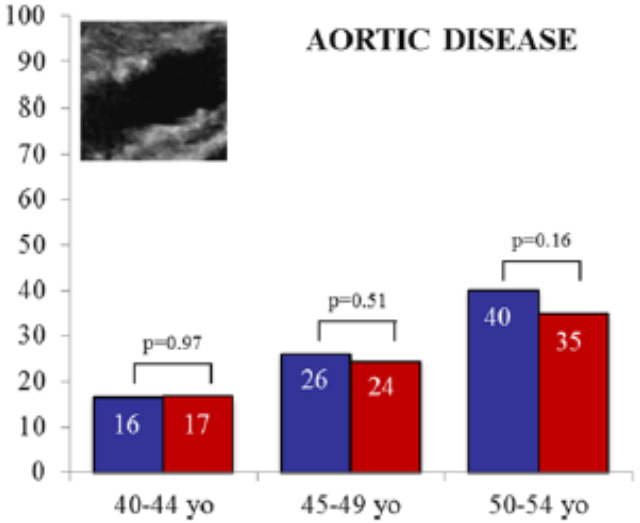
- Extension of atherosclerosis in carotid, abdominal aortic, and iliofemoral territories assessed by US and CAC assessed by CT
- Defined as presence of CAC ≥1 or plaque (focal protrusion into the arterial lumen > 0.5 mm or >50% of the surrounding intima-media thickness or a diffuse thickness > 1.5 mm)
- Classified as:
  - disease free (0 site affected)
  - focal (1 site affected)
  - intermediate (2-3 sites)
  - generalized (4-6 sites)
- 4184 asymptomatic participants, mean age, 45.8 years; 63% male
- Followed for 6 years
- 62% of participants had at least 1 risk factor, 18% 2 risk factors and 5% ≥ risk factors
- The most prevalent risk factor was dyslipidemia (42%, followed by smoking (21%), family history (16%), hypertension (12%) and diabetes (2%)

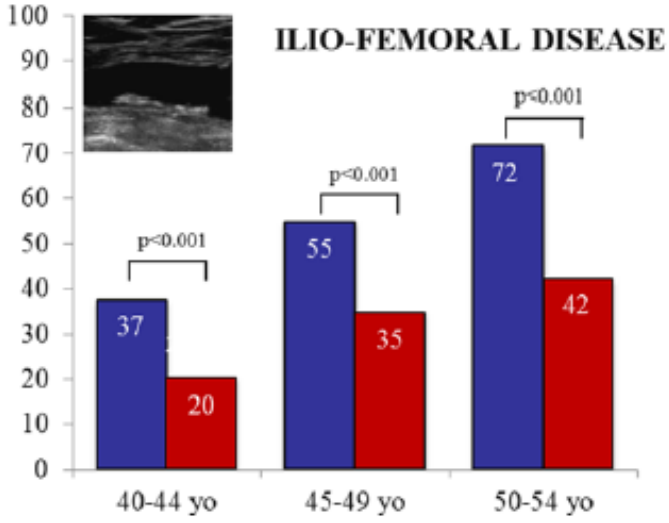
Fernandez-Friera L et al, Circulation 2015;131: 2104-2113

Prevalence of subclinical atherosclerosis was 63%: focal disease in 21%, intermediate disease 28%, generalized disease in 13%





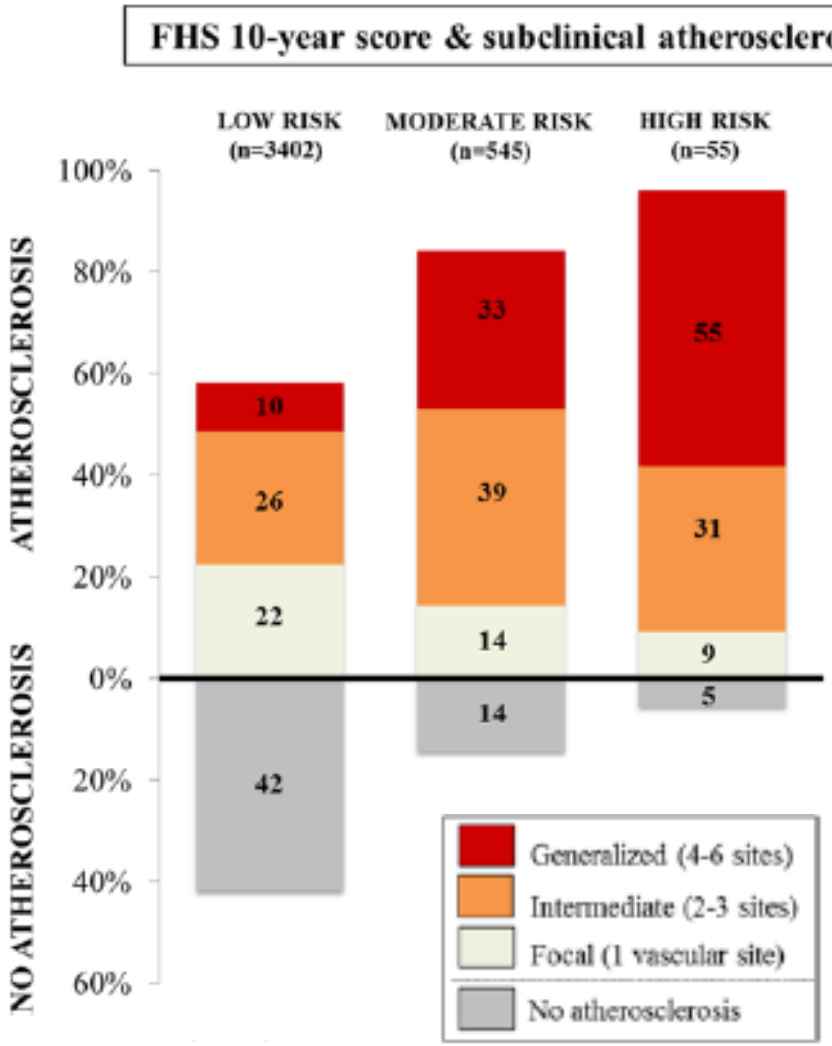


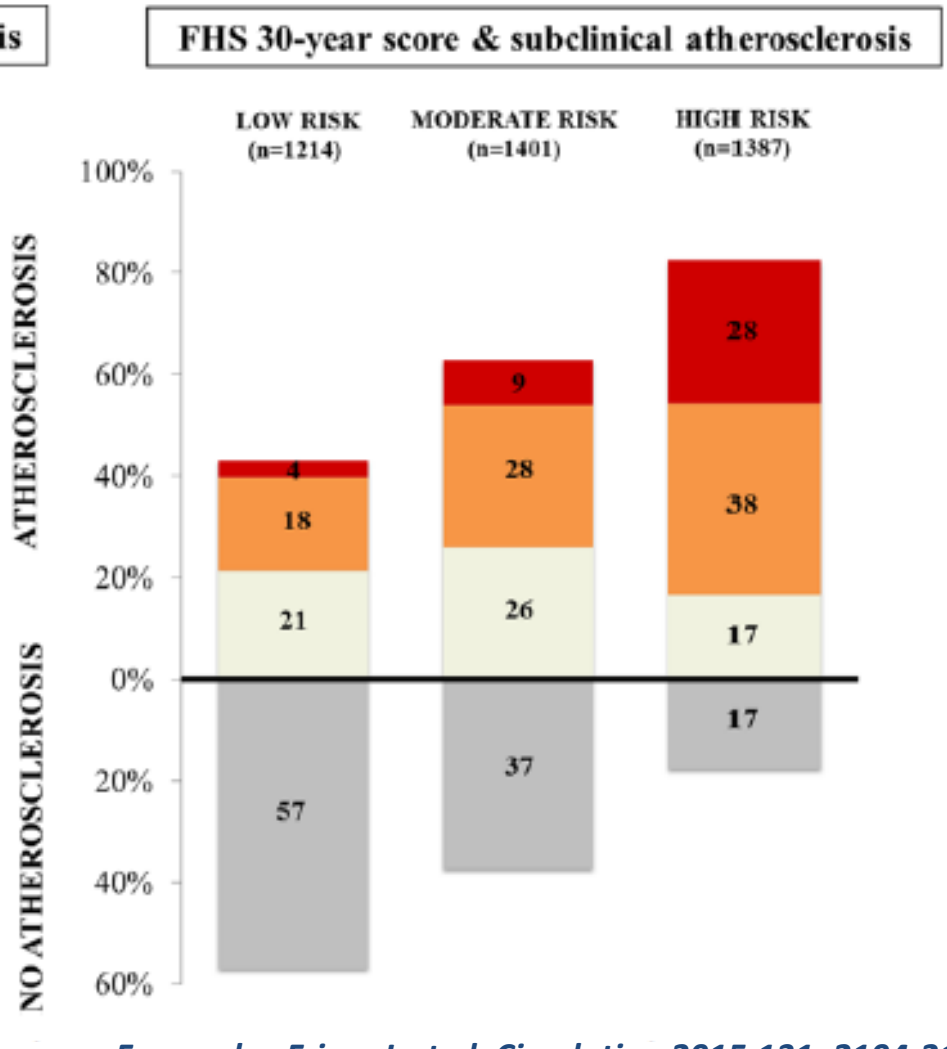


Fernandez-Friera L et al, Circulation 2015;131: 2104-2113

Distribution of subclinical atherosclerosis according to FHS risk

Mean FHS 10-year score in the PESA cohort was 6% and 85% of participants were at low risk

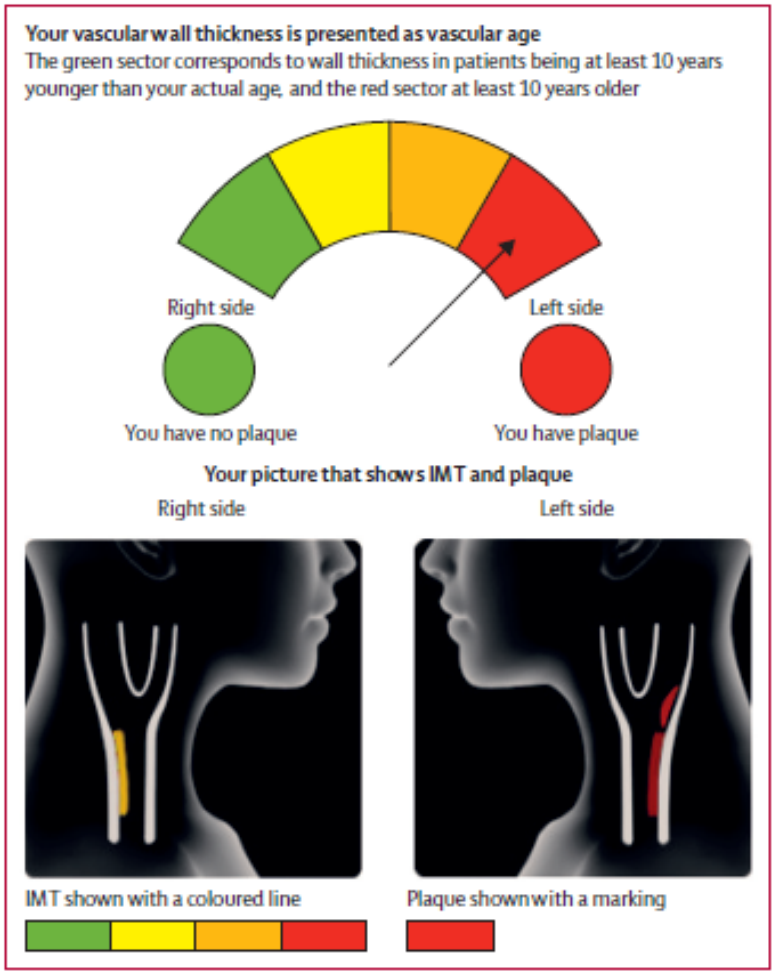


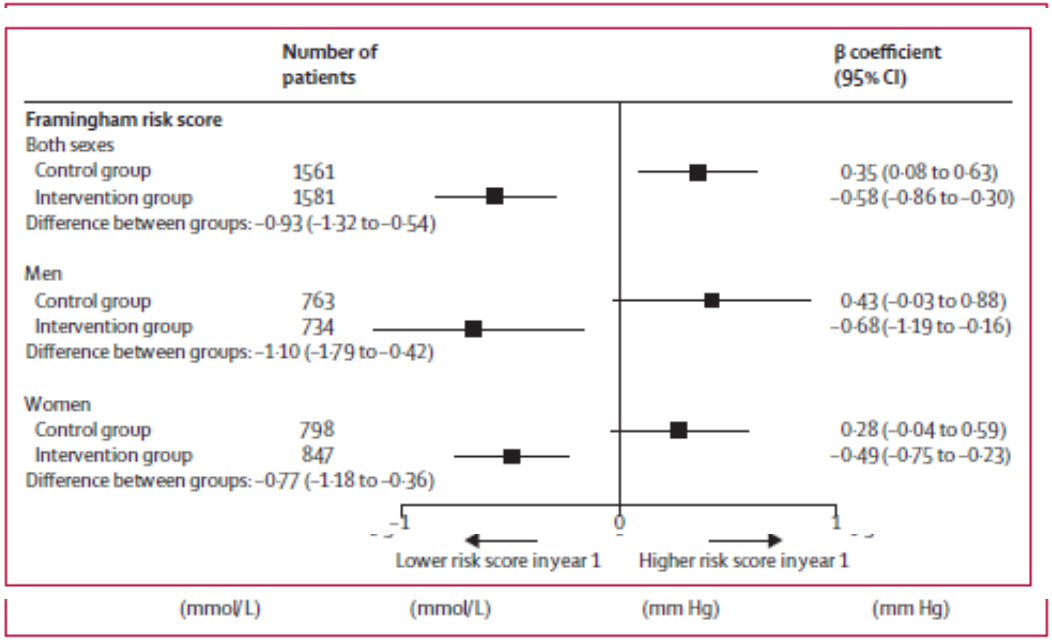


Fernandez-Friera L et al, Circulation 2015;131: 2104-2113

Visualization of asymptomatic atherosclerotic disease for optimum cardiovascular prevention (VIPVIZA): a pragmatic, open-label, randomised controlled trial

3532 participants randomized to intervention (1749) or to control group (1783)

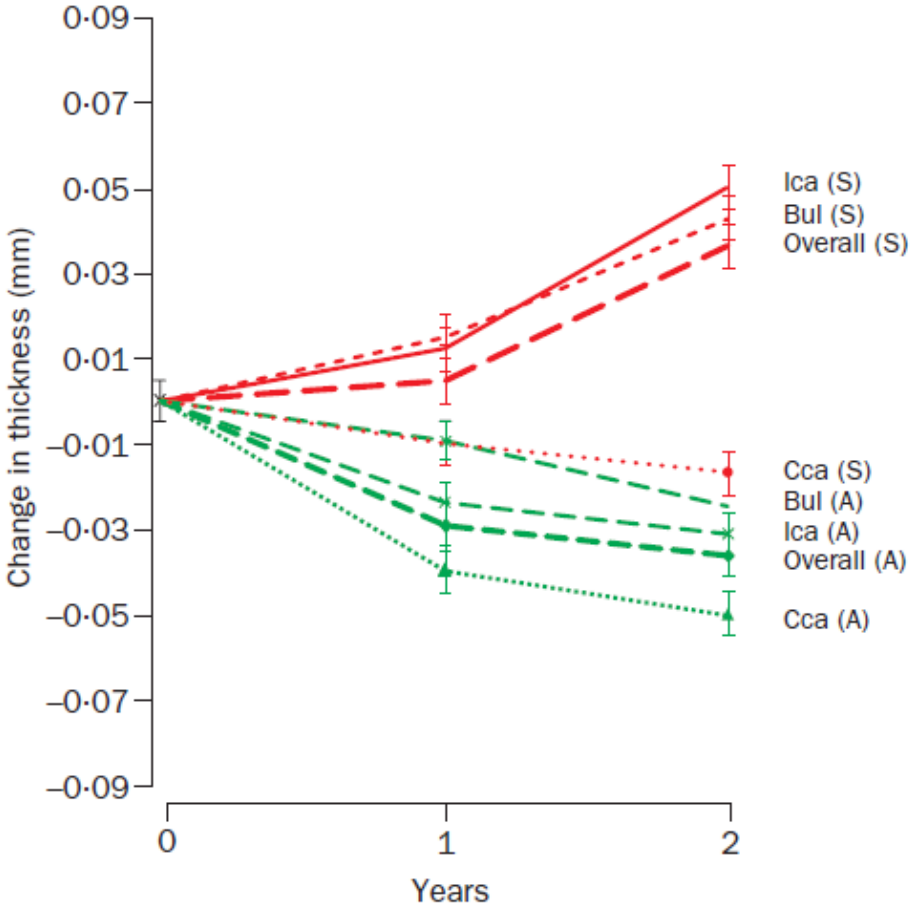




Naslund U et al, Lancet 2019;393:133-142

Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial

- ✓ 325 patients with familial hypercholesterolaemia randomized to atorvastatin 80 mg (n=160) or simvastatin 40 mg (n=165)
- ✓ Primary endpoint: change IMT over 2 years
- ✓ Regression of IMT was seen in 66% of pts in the atorvastatin group vs 42% pts in the simvastatin group
- ✓ The IMT change was correlated with % LDL reduction (P= 0.01)



Smilde TJ et al, Lancet 2001; 357: 577-581

Effect of Rosuvastatin on Progression of Carotid Intima-Media Thickness in Low-Risk Individuals With Subclinical Atherosclerosis

The METEOR Trial

984 individuals, with age (mean, 57 years) as the only risk factor or a 10-year FRS of less than 10%, modest CIMT thickening (1.2-<3.5 mm), and elevated LDL (mean, 154 mg/dL) randomized to rosuvastatin 40 mg or placebo

Table 3. Changes in the Primary and Secondary End Points

	Change in CIMT (95% CI), mm/y			*P* Value	
	Rosuvastatin (n = 624)	Placebo (n = 252)	Difference	Rosuvastatin vs Placebo	Within Rosuvastatin Group vs No Change
Primary					
Maximum CIMT for 12 carotid artery sites	–0.0014 (–0.0041 to 0.0014)	0.0131 (0.0087 to 0.0174)	–0.0145 (–0.0196 to –0.0093)	<.001	.32
Secondary					
Maximum CIMT (4 sites each)					
Common carotid artery sites	–0.0038 (–0.0064 to –0.0013)	0.0084 (0.0043 to 0.0124)	–0.0122 (–0.0170 to –0.0074)	<.001	.004
Carotid bulb sites	–0.0040 (–0.0090 to 0.0010)	0.0172 (0.0094 to 0.0251)	–0.0212 (–0.0306 to –0.0119)	<.001	.11
Internal carotid artery sites	0.0039 (–0.0009 to 0.0088)	0.0145 (0.0068 to 0.0221)	–0.0105 (–0.0196 to –0.0015)	.02	.11
Mean CIMT (4 sites)					
Common carotid artery sites	0.0004 (–0.0011 to 0.0019)	0.0088 (0.0064 to 0.0112)	–0.0085 (–0.0113 to –0.0056)	<.001	.64

Abbreviations: CI, confidence interval; CIMT, carotid intima-media thickness.

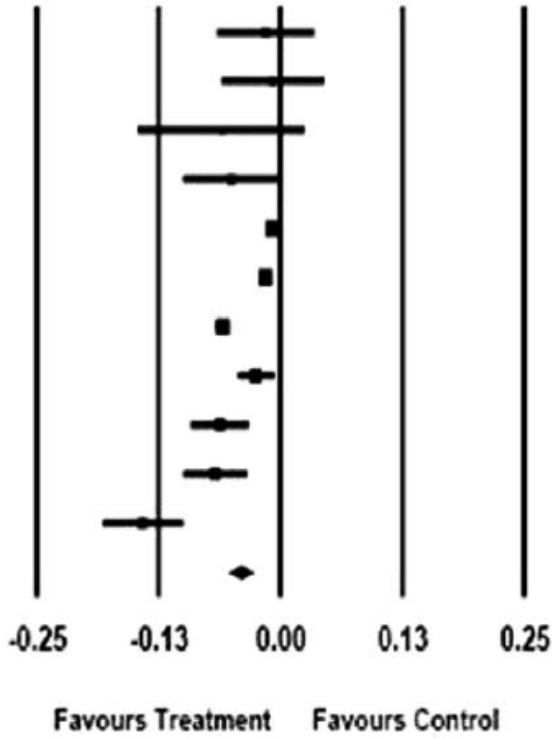
Crouse JR et al, JAMA 2007; 297: 1344-1353

Effects of Statins on Progression of Carotid Atherosclerosis as Measured By Carotid Intimal–Medial Thickness: A Meta-Analysis of Randomized Controlled Trials

3806 pts → 7 trials showed regression and 4 trials showed slowing of progression of CIMT

Model	Study name	Difference in means	Lower limit	Upper limit	p-Value
	Takahashi et al (simvastatin)	-0.015	-0.064	0.034	0.549
	Takahashi et al (pravastatin)	-0.008	-0.060	0.044	0.761
	Yu et al	-0.060	-0.144	0.024	0.164
	REGRESS Us Study	-0.050	-0.099	-0.001	0.046
	METEOR	-0.009	-0.011	-0.006	0.000
	ACAPS	-0.015	-0.016	-0.014	0.000
	ARBITER	-0.059	-0.065	-0.053	0.000
	BCAPS	-0.025	-0.043	-0.007	0.007
	LIPID	-0.062	-0.091	-0.033	0.000
	ASAP	-0.067	-0.099	-0.035	0.000
	HODIS et al	-0.141	-0.181	-0.101	0.000
Random		-0.040	-0.052	-0.028	0.000

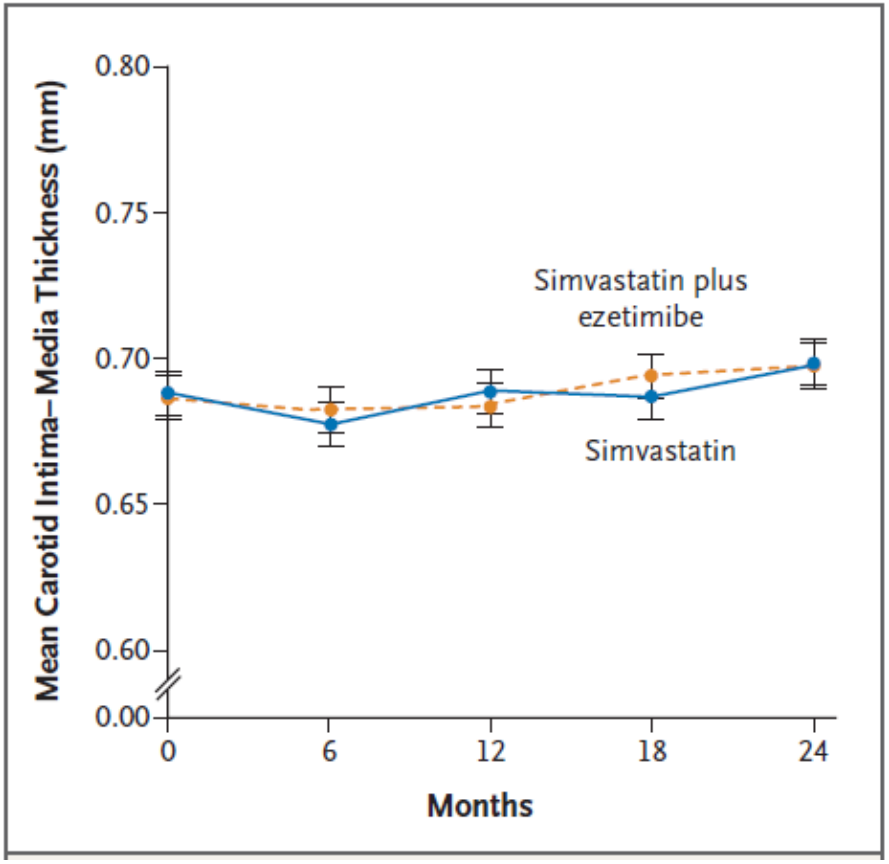
Statistics for each study



Bedi US et al, *J Cardiovasc Pharmacol Ther* 2010;15:268-73

Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia

720 patients with familial hypercholesterolemia randomized to daily therapy with 80 mg of simvastatin either with placebo or with 10 mg of ezetimibe



Kastelein JJ et al, *New Engl J Med* 2008;358:1431-43

Treatment of Asymptomatic Adults With Elevated Coronary Calcium Scores With Atorvastatin, Vitamin C, and Vitamin E

The St. Francis Heart Study Randomized Clinical Trial

Yadon Arad, MD, FACC, Louise A. Spadaro, MD, FACC, Marguerite Roth, RN, David Newstein, DrPH, Alan D. Guerci, MD, FACC

Roslyn, New York

OBJECTIVES We sought to determine whether lipid-lowering therapy and antioxidants retard the progression of coronary calcification and prevent atherosclerotic cardiovascular disease (ASCVD) events.

BACKGROUND The electron beam computed tomography-derived coronary calcium score predicts coronary disease events. Small, uncontrolled studies suggest that vigorous lipid-lowering therapy slows progression of coronary calcification and prevents coronary artery disease events, but controlled, scientific demonstration of these effects is lacking.

METHODS We conducted a double-blind, placebo-controlled randomized clinical trial of atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha-tocopherol) 1,000 U daily, versus matching placebos in 1,005 asymptomatic, apparently healthy men and women age 50 to 70 years with coronary calcium scores at or above the 80th percentile for age and gender. All study participants also received aspirin 81 mg daily. Mean duration of treatment was 4.3 years.

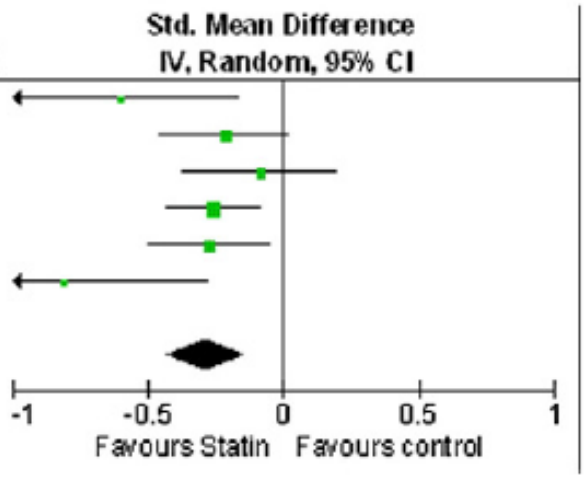
RESULTS Treatment reduced total cholesterol by 26.5% to 30.4% ($p < 0.0001$), low-density lipoprotein cholesterol by 39.1% to 43.4% ($p < 0.0001$), and triglycerides by 11.2% to 17.0% ($p \leq 0.02$) but had no effect ($p = 0.80$) on progression of coronary calcium score (Agatston method). Treatment also failed to significantly reduce the primary end point, a composite of all ASCVD events (6.9% vs. 9.9%, $p = 0.08$). Event rates were related to baseline calcium score (pre-specified analysis) and may have been reduced in a subgroup of participants with baseline calcium score >400 (8.7% vs. 15.0%, $p = 0.046$ [not a pre-specified analysis]).

CONCLUSIONS Treatment with alpha-tocopherol, vitamin C, and low doses of atorvastatin (20 mg once daily) did not affect the progression of coronary calcification. Treatment may have reduced ASCVD events, especially in subjects with calcium scores >400, but these effects did not achieve conventional levels of statistical significance. (J Am Coll Cardiol 2005;46:166–72)

Meta-analysis of trials examining the effects of statins on coronary atheroma

Study or Subgroup	Statin Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Brown (15)	-0.7	5.3	38	2.1	3.9	46	8.6%	-0.61 [-1.04, -0.17]
Herd (16)	0.5	9.1	129	2.5	9.2	132	19.9%	-0.22 [-0.46, 0.03]
Mizuno (17)	0.055	0.27	90	0.078	0.27	98	16.3%	-0.08 [-0.37, 0.20]
Nissen (1)	0.6	5.1	253	1.9	4.9	249	27.6%	-0.26 [-0.44, -0.08]
Waters (2)	0.05	0.13	146	0.09	0.16	153	21.5%	-0.27 [-0.50, -0.05]
Yamada (18)	-1.4	11.6	26	7.6	10.3	32	6.1%	-0.81 [-1.35, -0.27]
Total (95% CI)			**682**			**710**	**100.0%**	**-0.29 [-0.43, -0.15]**

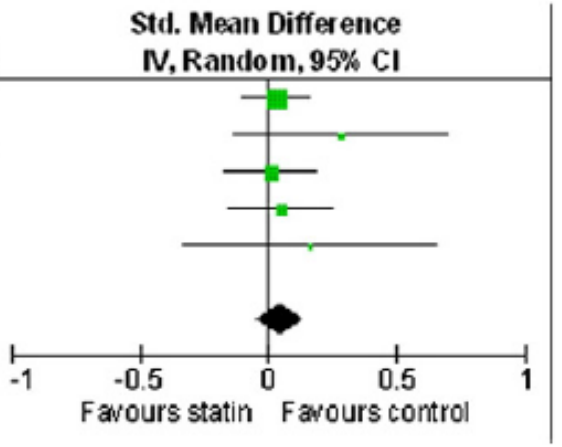
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.94$, df = 5 (P = 0.16); $I^2 = 37\%$
Test for overall effect: Z = 3.97 (P < 0.0001)



Meta-analysis of trials examining the effects of statins on coron. calcifications

Study or Subgroup	Statin Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Arad (10)	38	75	417	36	58	431	46.3%	0.03 [-0.10, 0.16]
Houslay (11)	0.234	0.231	39	0.167	0.238	49	4.7%	0.28 [-0.14, 0.71]
Raggi (12)	20.1	30.8	218	19.8	34.8	257	25.7%	0.01 [-0.17, 0.19]
Schmermund (13)	27	40.5	175	25	42.3	191	19.9%	0.05 [-0.16, 0.25]
Terry (14)	69	582	30	-27	601	32	3.4%	0.16 [-0.34, 0.66]
Total (95% CI)			**879**			**960**	**100.0%**	**0.04 [-0.05, 0.14]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.62$, df = 4 (P = 0.81); $I^2 = 0\%$
Test for overall effect: Z = 0.95 (P = 0.34)



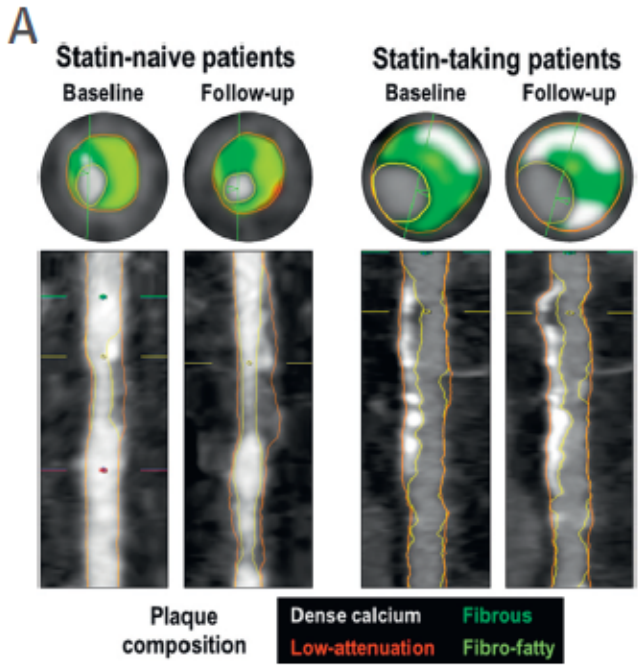
Henein MH, Intern J of Cardiol 2011;15331-35

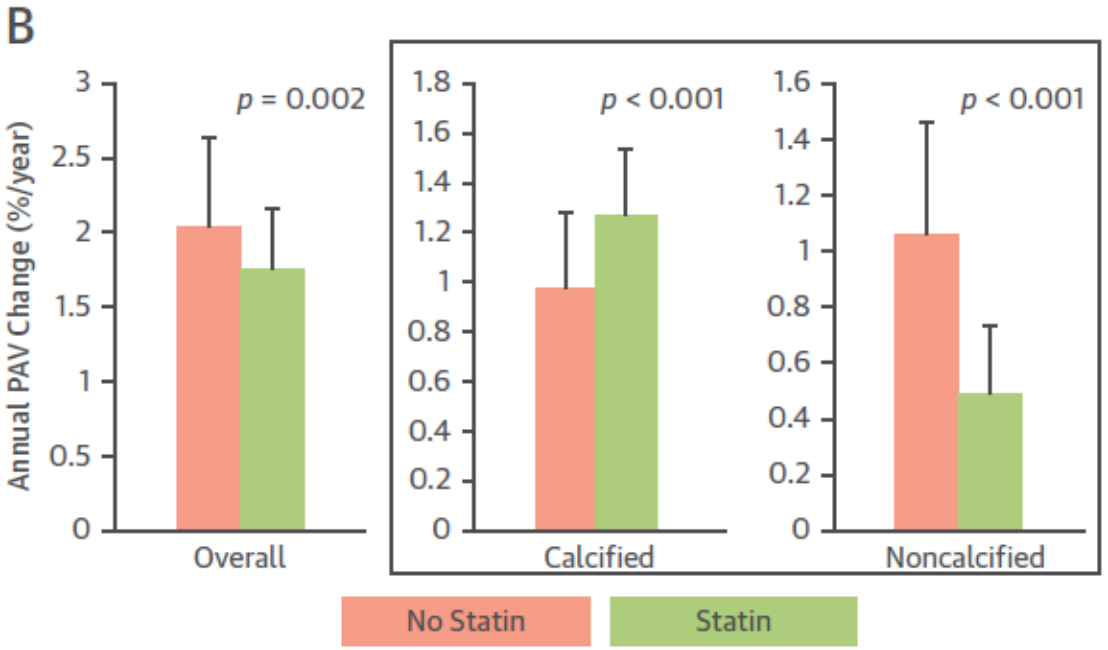
Effects of Statins on Coronary Atherosclerotic Plaques

The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) Study

Prospective registry of pts without history of CAD underwent serial coronary CTA

In 1,255 patients (60 ± 9 years of age; 57% men), 1,079 coronary artery lesions were evaluated in statin-naive patients (n = 474), and 2,496 coronary artery lesions were evaluated in statin-taking patients (n = 781)

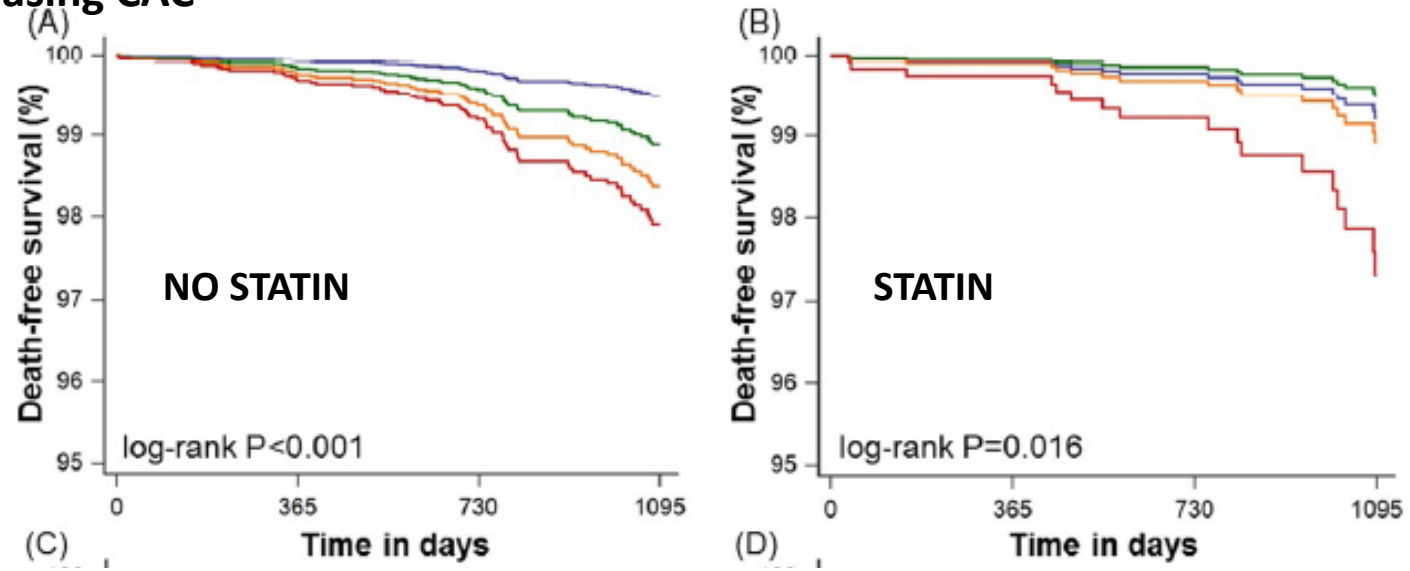




Lee SE, JACC Cardiovasc Imag 2018; *11:1475-1484*.

Usefulness of baseline statin therapy in non-obstructive coronary artery disease by coronary computed tomographic angiography: From the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) study

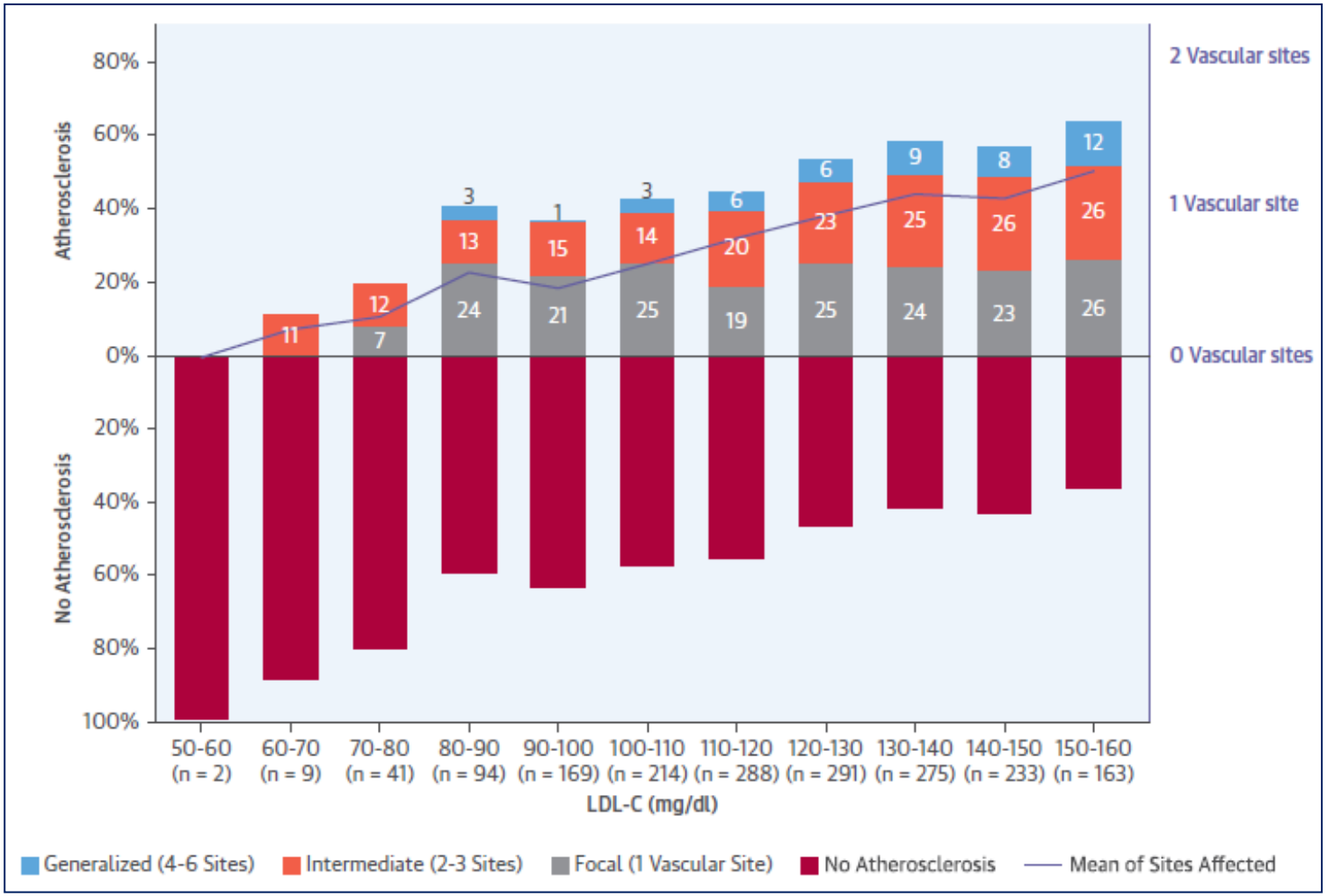
- ✓ **8,016 pts followed for a median of 2.5 years**
- ✓ **Patients not on statin therapy had a stepwise increased risk of all-cause mortality by CAC (CAC 1-99: HR 1.65, CAC 100-299: HR 2.19, and CAC≥300: HR 2.98)**
- ✓ **Conversely in pts on statin treatment, there was no significant increase in mortality risk with increasing CAC**



In panel A and B blue, green, orange and red lines indicate 0, 1-99, 100-299 and ≥ 300 CAC categories

Cho YK et al, PLoSOne **2018**

Which is the LDL target in patients with subclinical atherosclerosis?

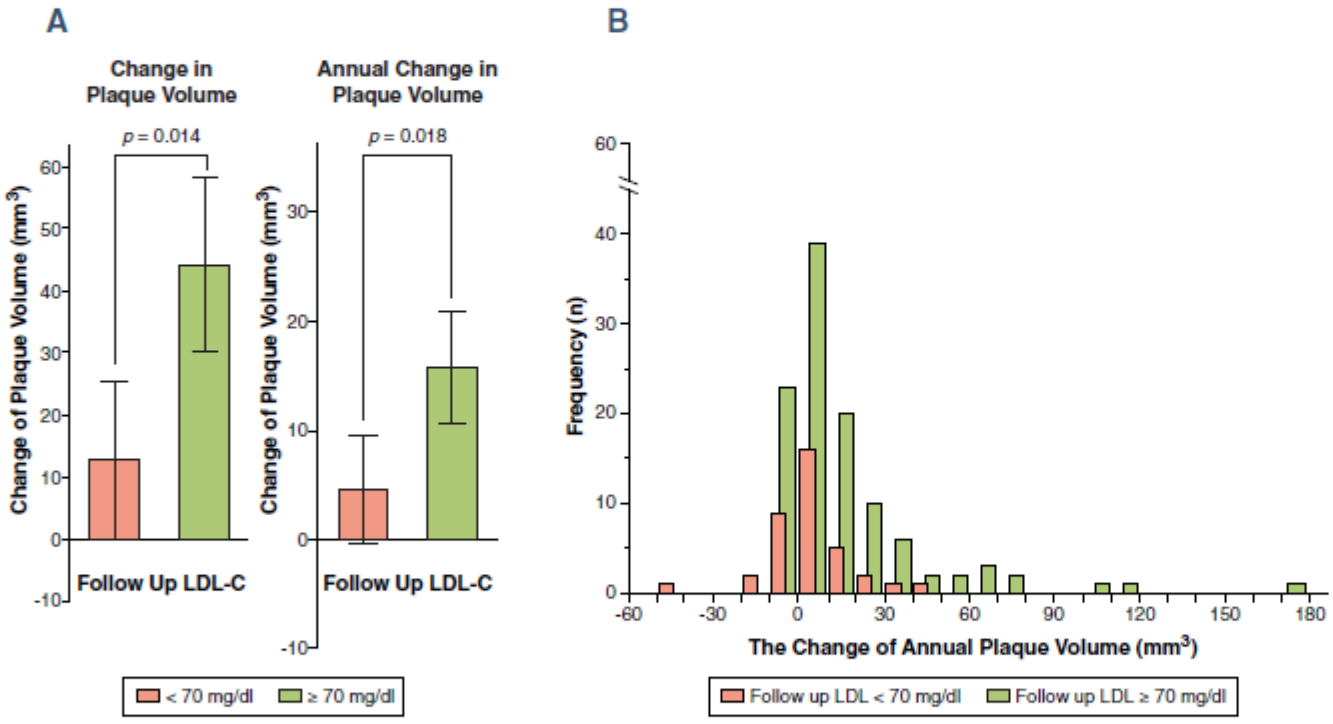


Fernandez-Frieia L et al, JACC 2017;70: 2979-91

Impact of Intensive LDL Cholesterol Lowering on Coronary Artery Atherosclerosis Progression

A Serial CT Angiography Study

FIGURE 5 Coronary Artery and Atherosclerosis Changes as a Function of LDL-C Control



Patients achieving a low-density lipoprotein cholesterol (LDL-C) <70 mg/dl demonstrated a lower progression in plaque volume compared with patients with follow-up LDL-C levels ≥70 mg/dl **(A)**. Likewise, the annual change in plaque volume was also attenuated for patients achieving low LDL-C <70 mg/dl level (the mean interscan period was 3.2 ± 1.1 years) **(A and B)**.

Shin S et al, JACC Cardiovasc Imaging 2017; 10:437-446

There is a role for aspirin in patients with subclinical atherosclerosis?

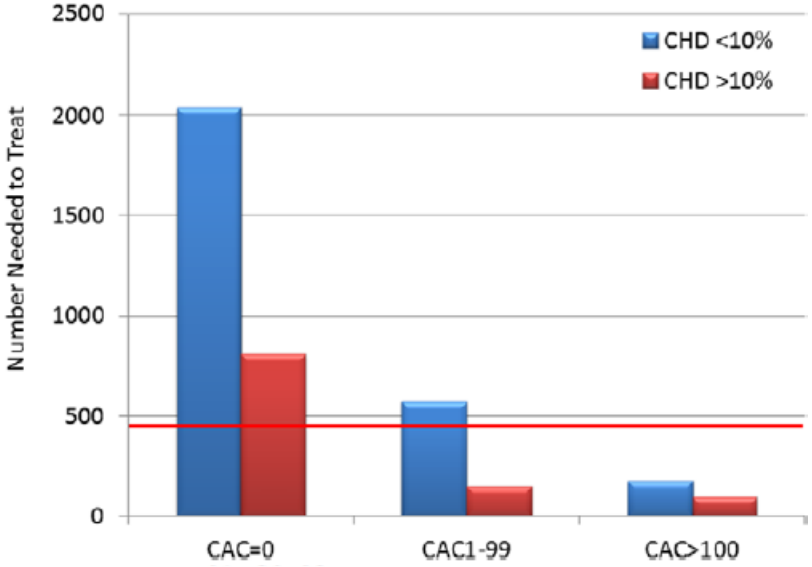
Potential Implications of Coronary Artery Calcium Testing for Guiding Aspirin Use Among Asymptomatic Individuals With Diabetes

2384 diabetic patients, underwent CAC assessment and with a FU of 5.6 years

Predicted 10-year CVD risk per guidelines	Number of individuals (%)	Number of deaths (%)	Mortality rate/1,000 person-years at risk	95% CI for rate
Low risk (<5%) "aspirin not recommended"	89			
CAC = 0	38 (42.7)	0	0	—
CAC 1–100	35 (39.3)	1 (2.9)	5.75	0.81–40.83
CAC >100	16 (18)	3 (18.8)	39.42	12.72–122.24
Intermediate risk (5–10%) "aspirin to be considered"	979			
CAC = 0	288 (29.4)	3 (1)	2.29	0.74–7.09
CAC 1–100	370 (37.8)	10 (2.7)	6.24	3.36–11.59
CAC >100	321 (32.8)	27 (8.4)	20.37	13.97–29.71
High risk (>10%) "aspirin reasonable"	1,316			
CAC = 0	209 (15.9)	6 (2.9)	6.59	2.96–14.67
CAC 1–100	374 (28.4)	26 (7)	16.32	11.11–23.97
CAC >100	733 (55.7)	86 (11.7)	28.60	23.15–35.33

Silverman MG et al, Diabetes Care 2012; 35:624-626

Use of Coronary Artery Calcium Testing to Guide Aspirin Utilization for Primary Prevention: Estimates From the Multi-Ethnic Study of Atherosclerosis



- **4229 participants from the MESA not on aspirin at baseline and free of diabetes**
- **Participants with CAC≥100 had favorable risk/benefit estimations for aspirin use while participants with zero CAC were estimated to receive net harm from aspirin**

CHD Risk	No. of Participants	5-Year CHD Event Rate (%)	Estimated 5-Year NNT	5-Year Estimated Absolute Increase in Bleeding Rate (%)	Estimated 5-Year NNH
<10%					
CAC=0	1907	0.27	2036	0.23	442
CAC=1–99	633	0.97	571		
CAC≥100	289	3.22	173		
≥10%					
CAC=0	454	0.69	808	0.23	442
CAC=1–99	460	3.82	146		
CAC≥100	486	6.07	92		

CAC indicates coronary artery calcification; CHD, coronary heart disease; MESA, Multi-Ethnic Study of Atherosclerosis; NNH, number needed to harm; and NNT, number needed to treat.

Miedema MD et al, Circ Cardiov Qual Outcomes 2014; 7:453-460

Take Home Messages

- Subclinical atherosclerosis is highly prevalent even in subjects classified at low risk using traditional score
- A multivascular approach, like the PESA protocol, is more sensitive for the diagnosis
- The identification of subclinical atherosclerosis plays a key role in defining the timing an the intensity of primary prevention pharmacological interventions
- Study results showed the efficacy of statins therapy in slowing progression/regression of IMT
- We don’t know the desirable LDL target in these patients, but probably “lower is better”
- Aspirin may be a reasonable option in patients with CAC > 100 and low bleeding risk